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MEDICINES EVALUATION BOARD

Post-approval regulatory learning about benefits and risks

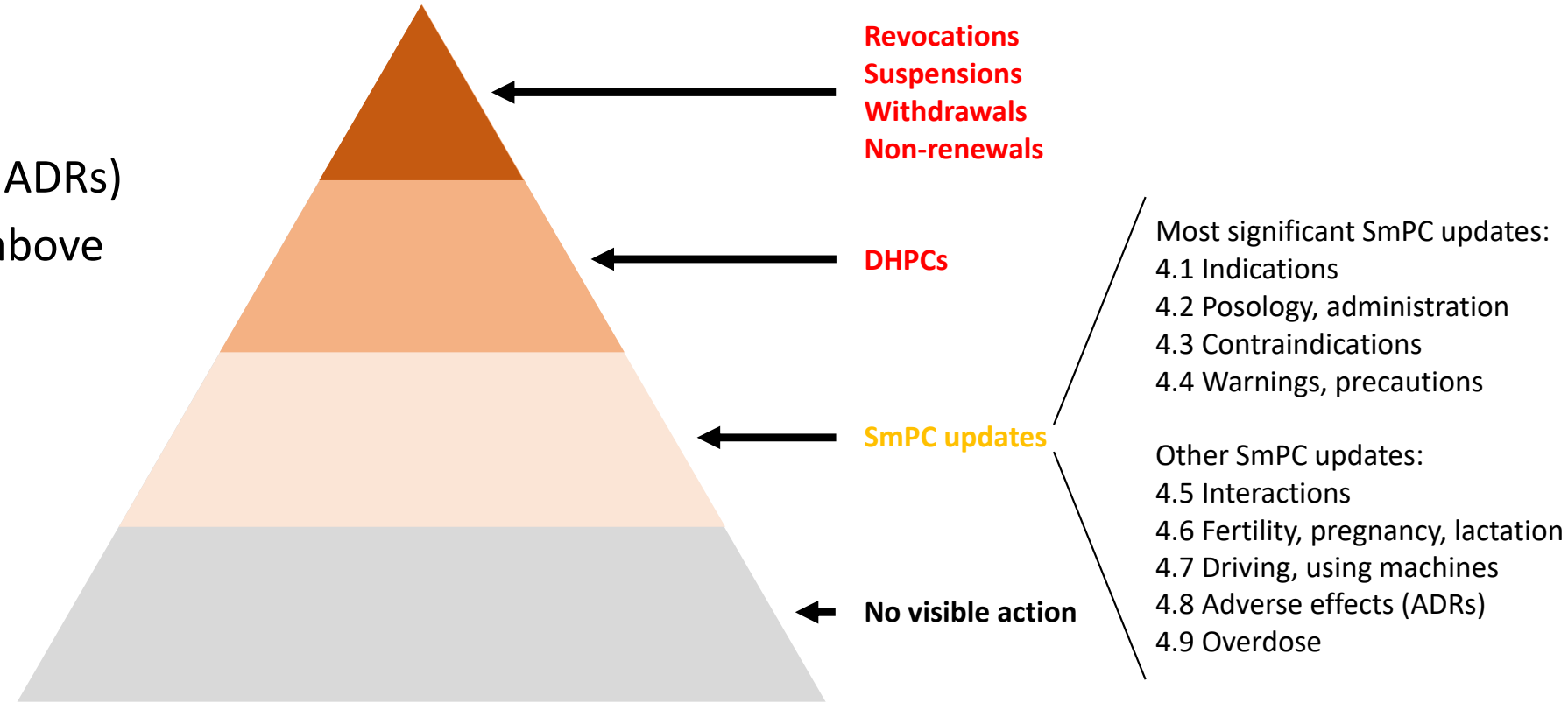
Lourens Bloem

GOOD MEDICINES USED BETTER

Previous research

Many studies assessed safety-related regulatory actions:

- Withdrawals
- DHPCs or similar
- Label updates
  (often only warnings and ADRs)
- Or a combination of the above



Adapted from Ebbers et al. Drug Saf 2012

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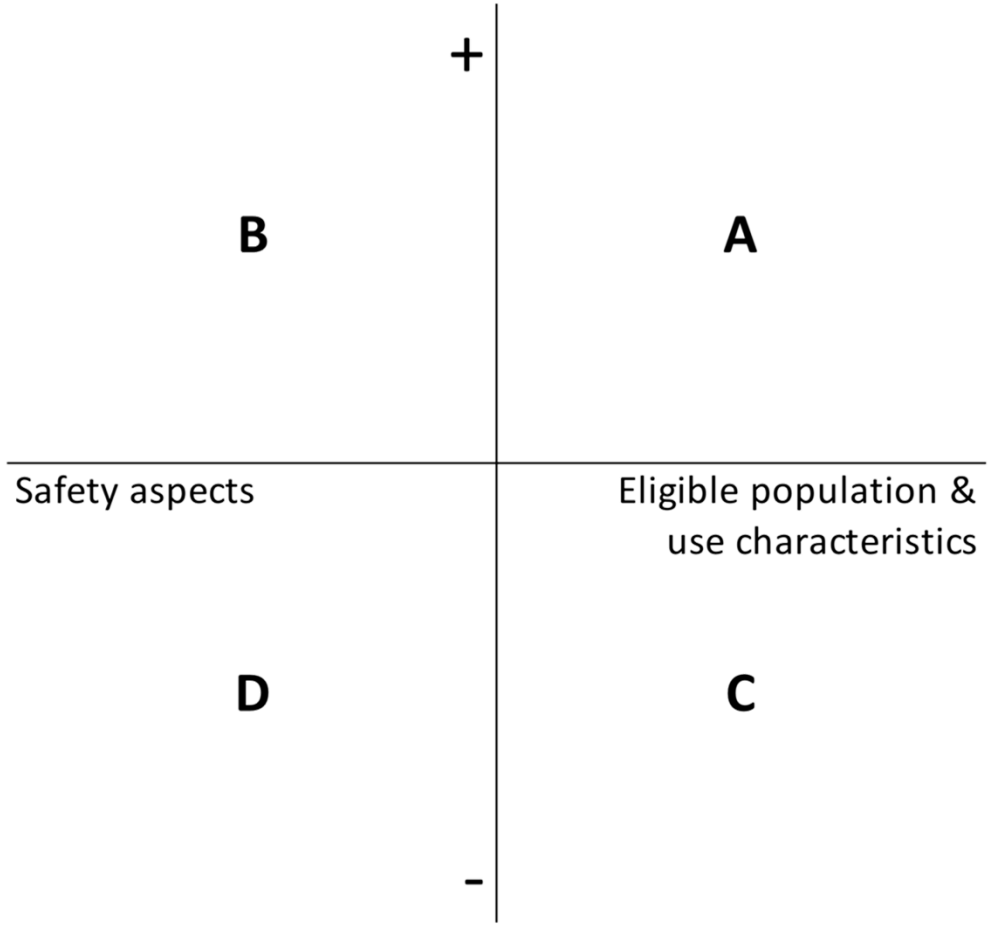
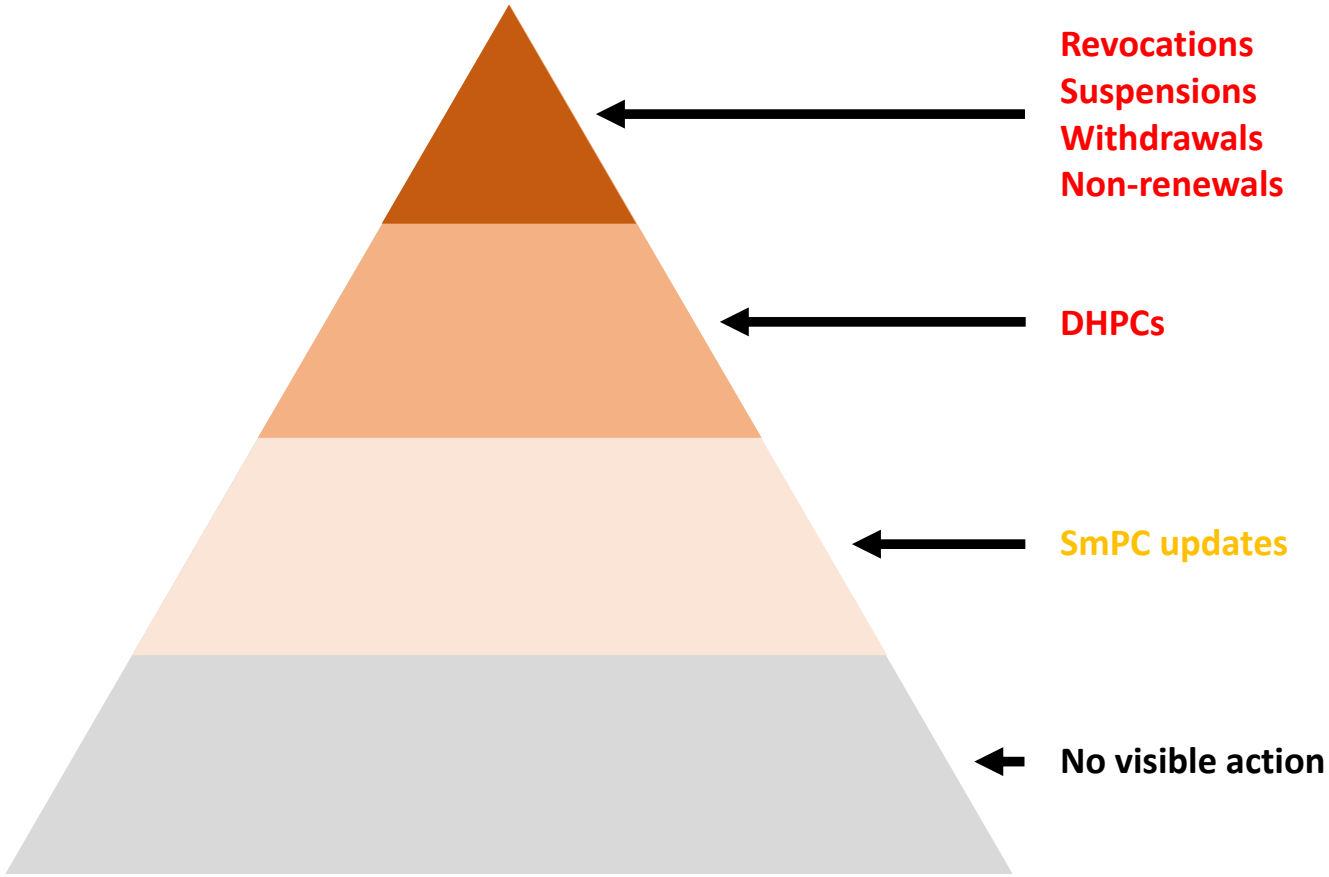
Following up on **new safety issues**

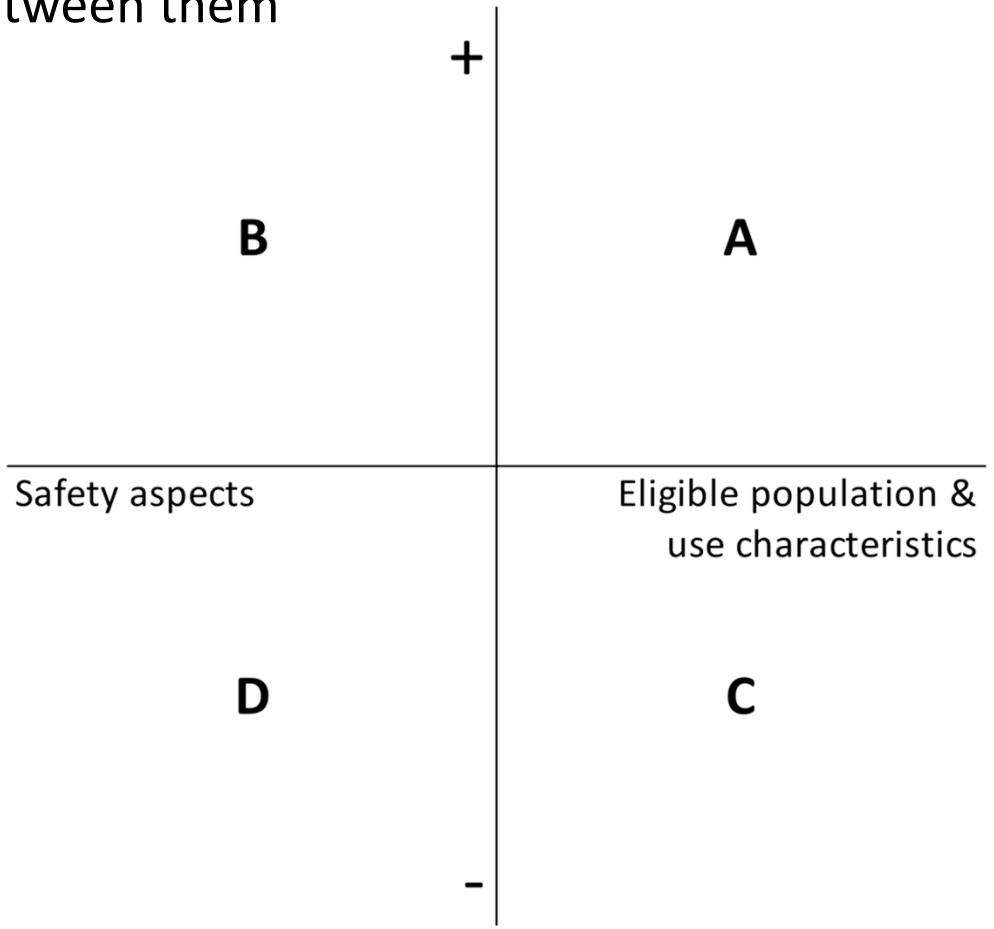
→ Quadrant D: negative impact on safety aspects



Aims

Characterize **all of these regulatory actions and relations** between them





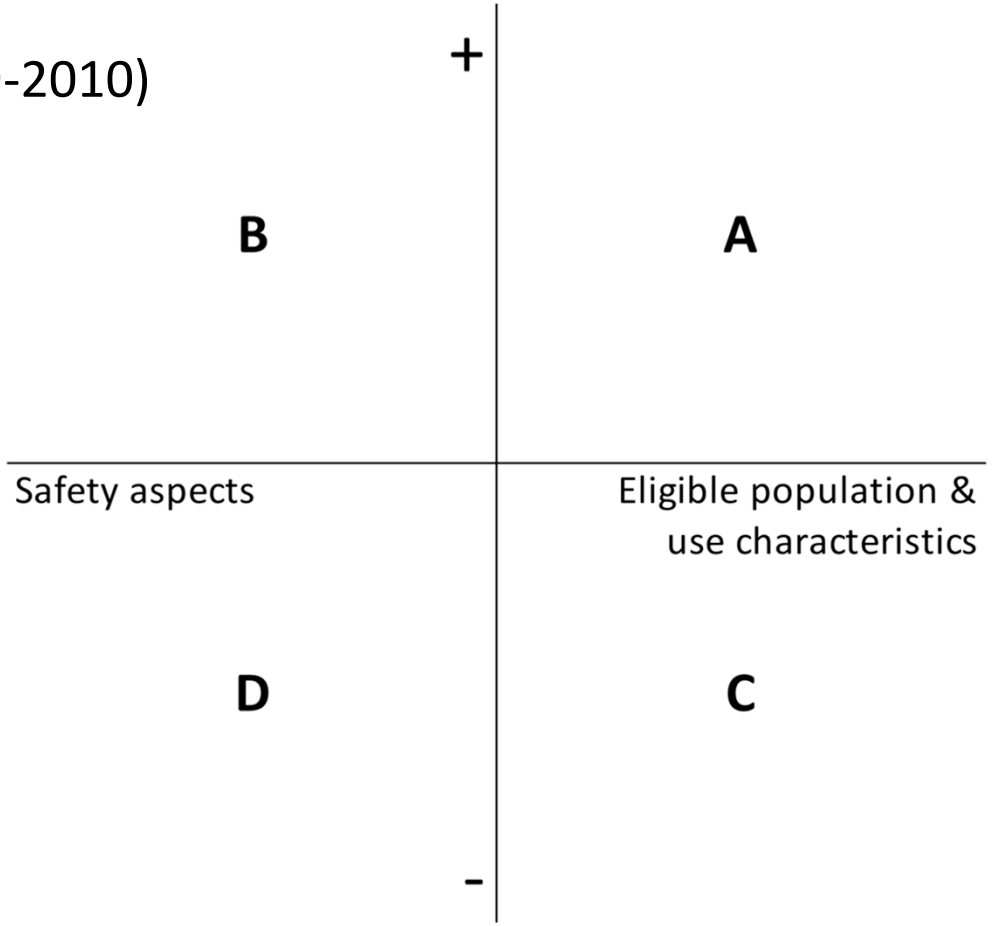
Methods

Drugs

- 40 EMA approved drugs with new active substance (2009-2010)
- Follow up until 1 July 2020 or withdrawal

Regulatory actions:

- From EPARs, SmPCs and NCA websites
- Assessed according to impact →
- Assessed for relations among SmPCs,
  i.e. those occurring simultaneoulsy (same procedure)



Results

Drugs

- 40 EMA approved drugs with new active substance (2009-2010)
- 5 drugs withdrawn for commercial reasons
- Median follow-up: 10.5 years (interquartile range 9.8-10.8 years)

Regulatory actions

- No revocations, suspensions, non-commercial withdrawals or non-renewals
- 14 DHPCs
- 361 updates to SmPC sections

Results

14 DHPCs, all with a negative impact

- 1 eligible population: communicated restriction of indication and contraindications
- 13 safety aspects: communicated new warnings

361 updates to SmPC sections

- 276 with a negative impact (76%)
- 85 with a positive impact (24%)

- 194 (54%) occurred simultaneously with another SmPC update

Results

Type of regulatory action	Positive impact		Negative impact		Total (*N* = 375)	
	A	B	C	D		
DHPCs	**–**	**–**	**1**	**13**	**14**	**4%**
SmPC updates	**73**	**12**	**14**	**262**	**361**	**96%**
Indications	48	–	2	–	*50*	*13%*
Posology, administration	16	3	2	4	*25*	*7%*
Contraindications	2	–	5	–	*7*	*2%*
Warnings, precautions	4	6	1	74	*85*	*23%*
Interactions	3	–	4	22	*29*	*8%*
Fertility, pregnancy, lactation	–	–	–	3	*3*	*1%*
Driving, using machines	–	–	–	5	*5*	*1%*
Undesirable effects (ADRs)	–	3	–	152	*155*	*41%*
Overdose	–	–	–	2	*2*	*1%*

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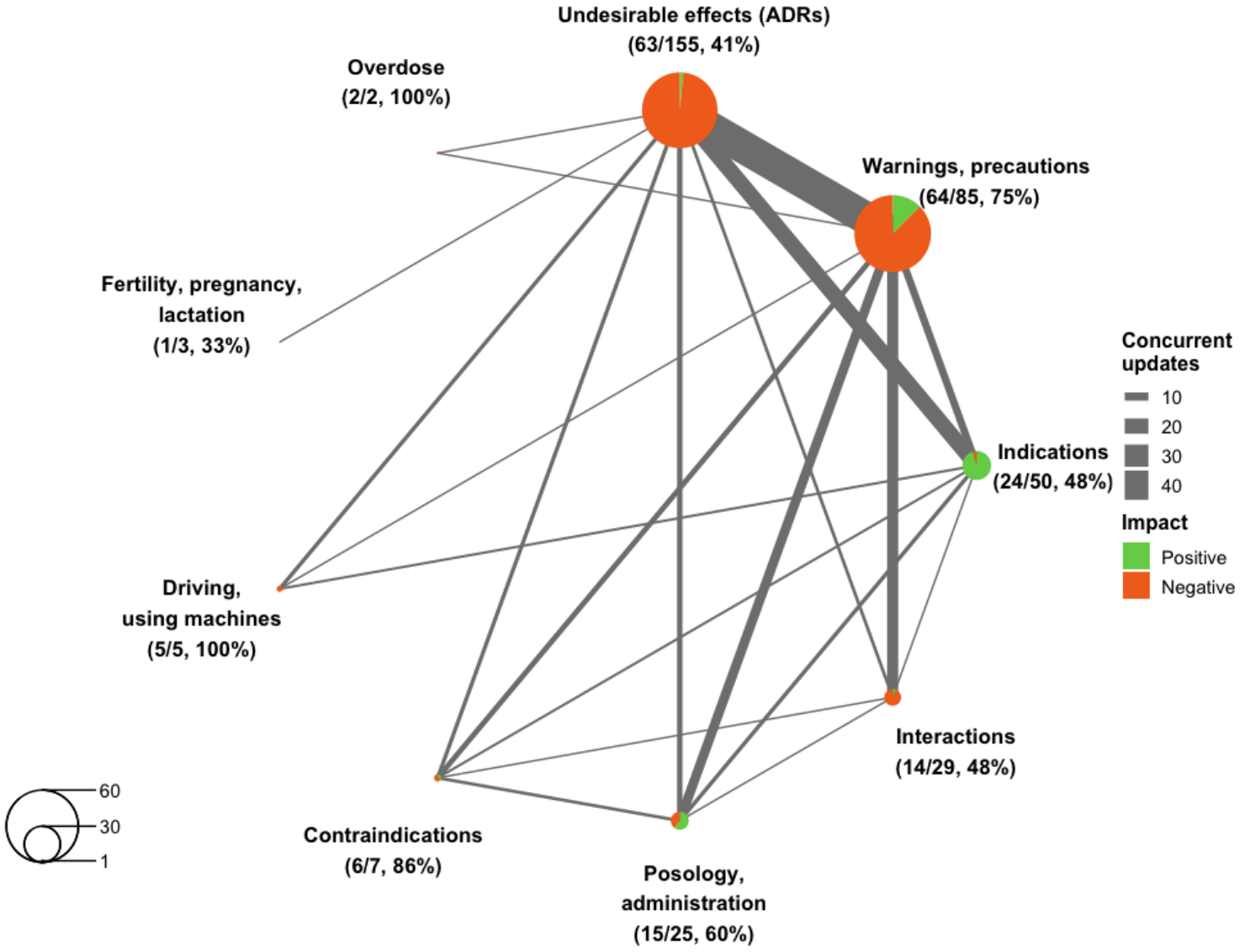
Results

194 (54%) SmPC updates occurred simultaneously with another SmPC update

Within 85 procedures:

- 55 all negative impact
  30 warnings/precautions + ADR
- 30 all positive or mixed impact, incl. 25 extended indications or positive posology changes that led to updated ADRs, warnings, precautions
  <u>Not always negative!</u>



Examples

- Victoza (liraglutide): new indication also led to a less restrictive warning regarding patients with congestive heart failure
- Resolor (prucalopride): broadening of the indication to use in men led to removal of a warning that use in men was not recommended due to a lack of efficacy and safety data
- Simponi (golimumab): new indication led to multiple ADR frequencies being decreased based on the new study data
- Brilique (ticagrelor): new indication led to moderate hepatic impairment no longer being contraindicated based on new study data

Key points

Majority of regulatory actions reflected a negative impact (77%), mostly safety-related

But

- 23% reflected a positive impact
- Some positively impacted the safety profile (removed ADRs, warnings, etcetera)

Also

- 54% of SmPC updates occurred simultaneously with other SmPC updates
- These not always reflected the same issue and impact

→ Role for further post-approval drug development in characterizing safety profiles

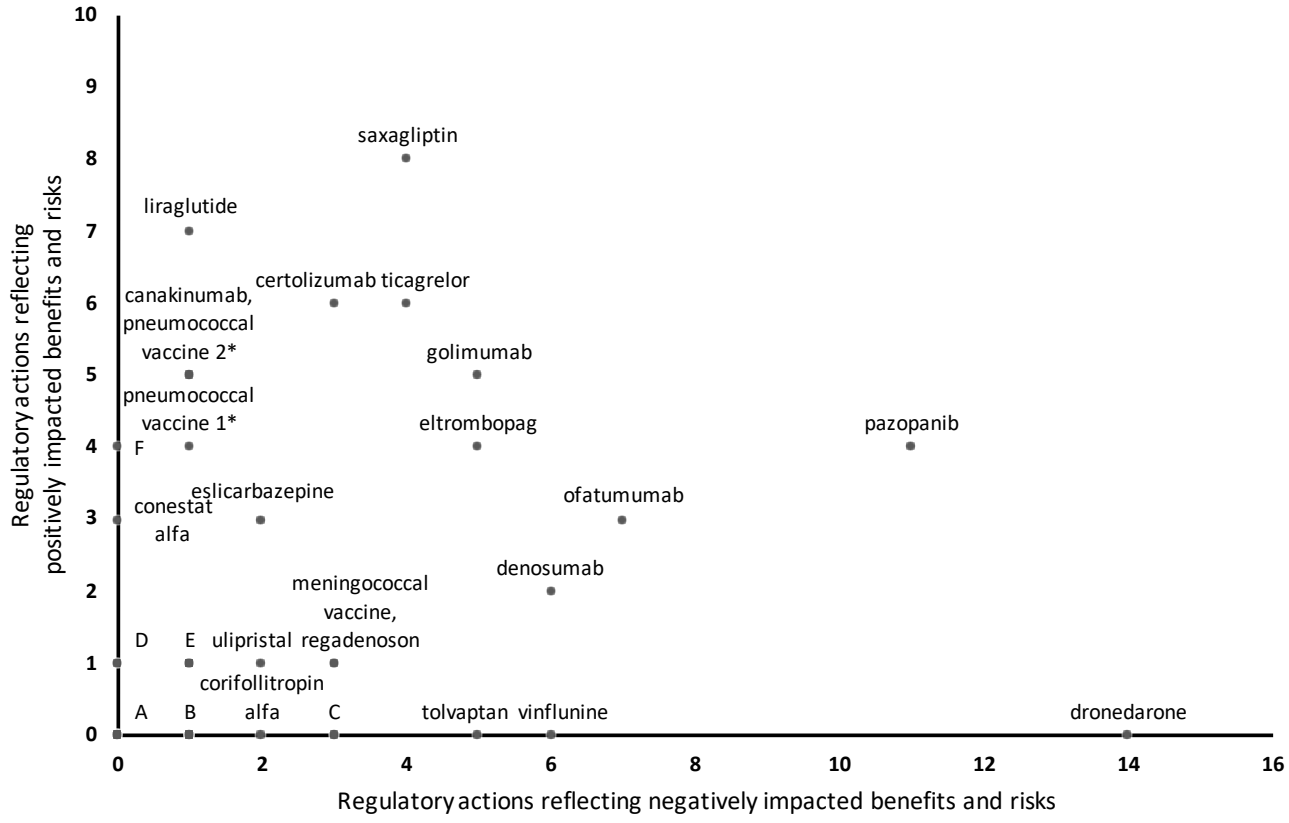
Future studies: should consider these findings for more complete and nuanced regulatory evaluations!

Further steps

Determine whether typical aspects of drug life cycles are associated with patterns of regulatory actions:

- Levels of exposure
- Levels of post-marketing drug development, e.g. new indications
- Levels of uncertainty, e.g. conditional approval

This could help regulators anticipate and allow further planning of regulatory activities



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